Compilation of Comments Received as of November 21, 2006 from Chartered SAB Members on draft SAB Report: *Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic*

Table of Contents

1. Dr. James Bus

Subject: Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic: And Advisory Report of the US EPA Science Advisory Board

Review comments prepared by: James S. Bus, PhD, DABT, Member, Chartered EPA SAB

Date: November 21, 2006

The EPA SAB Advisory Review Panel has conducted a very thorough and thoughtful review of the EPA analysis of the assessment of the carcinogenic effects of organic and inorganic arsenic. The Panel has offered detailed and clear responses to the charge questions of the review, and in general, has offered conclusions and recommendations that are fully supported by the draft report.

When the Review Panel has offered opinion that differs from those of the EPA review documents, it has provided extensive text and associated documentation that will prove useful for consideration by agency scientists. A particularly good example of this is the Review Panel's extensive commentary on the Mode of Action (MOA) of DMA, in which they provide useful analysis supporting their advocacy of an alternative non-linear cytotoxicity based MOA compared to the linear, oxidative-stress toxicity MOA proposed by EPA. This reviewer concurs with the Review Panel's alternative MOA recommendation and its implications for selection of a non-linear risk assessment model.

The letter to the Administrator and associated recommendation in the review indicates the Panel concurs *for now* with the EPA's proposal to apply a linear risk assessment approach for iAs. However, the Panel's review provides extensive commentary in response to charge question B3 (pp. 29-37) suggesting that animal, associated in vitro evidence, and even human genotoxicity data are highly suggestive that iAs should be expected to have a threshold. Similarly, much of the Panel's analysis of the epidemiology data (see section 3.5.2; p. 48-50) illustrates its weaknesses in illuminating the shape of the dose response below 100 ppb iAs exposure. The Panel goes on to suggest useful directions for further characterization of the epidemiology that ultimately might define future refinements in selection of risk assessment models for cancer risk of iAs. However, both the letter to Administrator and the primary conclusions presented in the Executive Summary do not seem to reflect the Panel's overall tone regarding their implied concerns surrounding use of a linear risk evaluation assessment of iAs-induced human cancer. The Panel should consider if their analysis is sufficient to suggest that the Agency, for the sake of transparency to future risk management decisions, consider developing alternative non-linear approaches to the evaluation of iAs carcinogenicity, and further, pointing to key data that, if generated, would be sufficient to justify both the use and selection of such alternative approaches.

Specific comments:

Letter to the Adminstrator, p.2, ll. 22-27, ll. 37-38: The statements here do not seem to adequately capture the tone of the review regarding iAs cancer risk, i.e., that further research into the animal mode of iAs and exploration of human epidemiology at <100 ppb iAs may well steer the future risk assessment to non-linear alternatives.

Executive Summary:

p. 6, ll. 4-12: This summary does not seem to adequately reflect the strength of conclusions reached in the main body of the review on p. 36, ll. 37-38 and p.37, ll. 1-4 regarding the likelihood that iAs cancer may involve a threshold response.

Review Body:

p.30, Table 1: Should altered DNA methylation be listed?

p.34, l.27: The description of theWaalkes et.al study might benefit from an expanded description of the dose-response, if conducted, in this study, and its implications for selection of risk models.

p.37, ll. 1-4: The review is perhaps a bit inconsistent with respect to its recommendation to use a non-linear model for DMA based entirely on animal evidence (appropriate!) and essentially no epidemiology, but proposes retaining application of a linear model for iAs even though both animal MOA and human genotoxicity data suggest potential non-linear outcomes and epidemiology data if viewed as "lacking or problematic". However, I concur with the conclusion that resolution of this issue through future research is "extremely important", a conclusion intensity that perhaps could be amplified in the both the Letter and the Executive Summary conclusions and recommendations.

p.39, ll. 21-25: The Panel indicates the studies of Gur et.al. would be very valuable in evaluating DMA MOA, but must be published and/or peer reviewed in order to fulfill that promise. This important conclusion is missing from the Executive Summary.

p.43, ll. 27-36: This conclusion provides excellent future research direction.

p.45, l. 30: If the toxicity/carcinogenicity of DMA is indeed due to its reduction, and this process is "saturable" as suggested here, it does indeed indicate potential "non-linear" toxicity responses, but not necessarily threshold-based responses? Saturation of reduction would seem to limit the upper-end responses of the dose-response, i.e., causing a plateau due limitation in the amounts of toxic reduced DMA?

p.46, ll. 22-24: This wording seems a bit odd, and perhaps could more directly state that EPA's position on a linear oxidative stress MOA is likely not defensible and should not be used.

2. Dr. Deborah Cory-Slechta

Comments on Chartered SAB Review of the Draft SAB Arsenic Review Panel Report

General Comment:

The Panel is to be congratulated for a very thorough response to a complex and extensive set of questions. It is clear that the Panel gave quite careful consideration to all of the questions. Some general suggestions are addressed at making the document more readable.

1. The conclusions in many sections get lost in the presentation of the arguments presented. For some charge questions, the conclusions are presented first, followed by text. In other sections, they appear in the midst of the text, and in some cases, they appear at the end. It would be useful to have a more consistent approach. In addition, it would be useful to change the formatting of the document to highlight those conclusions of the panel that are the specific answer to the charge question.
2. The sections describing MOAs include little in the way (for the most part) of direct comparisons of dose levels, i.e., they don't generally compare the effects at which these various observations occur, but rather present descriptions, e.g., 'low' etc. This section would probably be more useful if such information were presented, recognizing the difficulties and lack of direct comparisons in some cases. But it would further strengthen the arguments for the answer arrived at by the Panel.
3. Page 29-37 It would be very helpful to readers to have this section written with some conclusions at the end of each paragraph or after related paragraphs. It currently reads as a presentation of a significant number of studies, but the basis for their presentation is not clear, and the points that are attempting to be made by this section are being lost. This section could either include sub-titles that specifically state those conclusions or some other mechanism of making clear the basis for the inclusion of this material.
4. p. 19. Lines 1-18. It seems somewhat strange that statements are made about the potential for less severe outcomes in humans base don the fact that there is no metabolism to trimethylarsine species given that there is no statements cited that it is the TMA species that are more toxic or cause the toxicity. In the absence of that information, it doesn't seem appropriate to make that assumption. The answer to this is actually presented on p. 22, lines 31-37; this information should either be moved up or included in the response on p. 19 as well.
5. p. 46, lines 16-18, not a sentence.
6. p. 49, line 22, delete space between 'relations' and hips'
7. P. 58-61. Response to charge question D5. The answer seems to be to carry out sensitivity analyses, which is listed as a non-bolded two word phrase on p. 60, line 12.

3. Dr. Baruch Fishchoff

No comments

4. Dr. James Galloway

I have read the report and I have no comments.

5. Dr. Rogene Henderson

Comments of Rogene Henderson, Nov.17, 2006

I have reviewed the letter and the executive summary of this report.

a) I found the report to be highly responsive to the charge questions. Each question was discussed and the SAB Panel provided a clear response.

b) The draft report was clear, logical and easy to read. It is well-organized around the charge questions.

c) I am still reviewing the body of the report. The parts I have read support the conclusions given in the letter and in the executive summary.

6. Dr. Jill Lipoti

I have reviewed the draft report, Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic. I have no comments. The charge questions were adequately addressed.

7. Dr. Meryl Karol

This is an excellent draft report that effectively addresses the charge questions. The report is logical and clear, and its conclusions are supported in the text of the report. The following points are suggested for clarification/grammatical considerations:

- Letter – correct grammar, p. 2, line 22 change is to are; and line 25, but they the data do fit with a linear model.
- p. 34 line 28, unclear what is meant by "the document".
- p. 34 line 29, should read neither iAsIII nor iAsV is a are complete ….
- p. 35, last sentence. Do the authors wish to imply that all As species contribute to the toxicity in tissues. I suggest the authors consider

  rewording line 19 as follows "from all diverse species present in that tissue.

8. Dr. Michael McFarland

SAB Report: Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic: An Advisory Report of the US EPA Science Advisory Board

McFarland Comments

In general, the SAB Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic was well written, concise and provided specific recommendations for ensuring that the best science is utilized by the Agency in assessing the human health risks associated with Dimethylarsinic Acid (DMA) and inorganic arsenic. The report furnishes full and complete responses to each of the Agency charge questions and, where appropriate, the Panel provides supplemental information and recommendations that the Agency should consider in establishing the carcinogenic human health risks associated with organic and inorganic arsenic. The following are my specific comments regarding the report.

The cover letter provides a clear and unambiguous summary of the salient points found in the body of the report. The Panel provides a clear rationale for their support of several Agency recommendations including the use of bladder tumor data from DMA rat bioassays for human cancer risk assessment, application of Taiwan epidemiological data as the basis for human cancer risks associated with inorganic arsenic as well as the use of the low dose non-linear extrapolation approach (and use of uncertainty factors to capture variability and interspecies differences) for estimating the cancer risks associated with DMA.

The Executive Summary was well written and provides a clear synopsis of the Panel's findings and recommendations from the body of the report. Information found in the Executive Summary was effectively distilled and presented in the cover letter. The Panel is applauded for highlighting many of the key uncertainties associated with extrapolation of current animal data sets for use in modeling the potential carcinogenic effects of DMA and inorganic arsenic in humans. The Panel is also commended for its encouragement of the Agency to conduct sensitivity analyses to evaluate the performance of arsenic cancer risk models.

The body of the report provides well written and comprehensive responses to the Agency charge questions. In crafting its responses to charge questions, the Panel furnishes cogent and scientifically defensible arguments in support and, in some cases, opposition to the Agency's position on specific science issues. Moreover, where appropriate, the Panel cites extensive peer-reviewed references that support its consensus findings and recommendations.

9. Dr. Stephen Roberts

Overall, I found the SAB report to be responsive to the charge questions, and the conclusions to be logical and supported by information in the body of the report. There

were a few aspects of the report that could be improved, however, in my opinion. These are outlined in the comments below.

Pg. 18, lines 14-15, "… we do not expect to find significant amounts of MMA or iAs as products of DMA^V metabolism …": It would be helpful to include a statement about empirical evidence available to support this contention (e.g., measurements of MMA and iAs in tissues or urine after DMA administration). If empirical evidence is lacking, this should be acknowledged.

Pg. 22, lines 36-37, "This uncertainty should be properly addressed in the risk assessment for DMA^V exposure in humans.": Addressed how? This statement would be more helpful if accompanied by more explicit direction or at least an example.

Pg. 26, line 6, "Rather, the MOA is likely to be sustained cytotoxicity followed by genomic instability as a result of stress-related proliferation." The report lacks a clear articulation of the experimental evidence that supports this MOA. What appears in this paragraph reads more like a hypothetical construct. Later in the paragraph, the report states (lines 13-14), "In the case of arsenite, this would involve such factors as (See also section 3.3.3)." but it is unclear why observations with arsenite are necessarily relevant to the MOA for DMA^V bladder tumors in rats.

Pg. 31, lines 4-5, "... cause chromosome breakage, possibly mediated by ROS-induced DNA strand breaks.": Other sections conclude pretty strongly that ROS are not involved in the MOA for DMA^V. Does this statement contradict those statements elsewhere?

Pg. 37, line 24, "This question indirectly raises the issue as to the largest source for uncertainty for DMA^V risk assessment – conventional interspecies extrapolation or extrapolation across various forms of arsenic.": The report then follows with a list of various uncertainties. There is one uncertainty that doesn't seem to be contemplated in the report – namely, the possibility that *in addition* to an MOA based on repetitive cytotoxicity that gives rise to bladder tumors in rats, DMA^V also shares the MOA(s) of iAs that produce cancer in humans. As the report notes, there are no epidemiological studies of DMA^V exposure in humans with which to evaluate this possibility, and studies in rats are not particularly informative since they don't respond to iAs in conventional bioassays. There is room to speculate that DMA^V doesn't share the iAs MOAs (e.g., because of the diminished spectrum of arsenic metabolites from DMA^V compared with iAs exposure), but it is only speculation because the iAs MOAs are not clearly defined. This uncertainty should have been addressed in the report.

Pg. 38, lines 21 -22, "… laboratory animal studies have shown that DMA^V is not absorbed well – approximately 80% of a dose of the parent compound is excreted in a short time after exposure …": The two statements appear contradictory. Excretion of 80% of a dose shortly after administration, unless the dose is injected, suggests extensive absorption.

Pg. 45, lines 31- : Unpublished data are cited here to support an argument concerning linear versus non-linear approaches. Previously in the report (pg. 39), data from Gur et al. were mentioned in another context, with the statement that these data "… were never published and thus cannot be critically evaluated by the Panel. … Reliance on these studies would be stronger if the studies had the benefit of peer review." This gives the appearance of inconsistent standards regarding the acceptability of unpublished data in the SAB review.

Minor editorial comments:

Pg. 7, lines 6-7: Suggest revising to read " … in the Panel's complete response to charge question C1." That will make it clearer to the reader to look elsewhere in the document for these details.

Pg. 9, line 7: Delete "differences" at the end of the line.

Pg 27, line17, "The MOA outlined above …": Which MOA? The previous sections describe different possible MOAs.

Pg. 44, line 17: Suggest removing the comma after "µg/L"

Pg. 45, lines 13-15: It would be helpful to refer the reader to the previous section where the rationale for this statement (i.e., the rejection of ROS-induced DNA damage in the MOA for DMA^V carcinogenesis) is provided.

10. Dr. Thomas Theis

(a) Answer to the charge
In general the Panel has responded to the charge questions thoroughly and completely. Because of my background I focus more directly on the questions under "D" because these relate more directly to issues of uncertainty, variability, precision, and accuracy (as related to low-dose extrapolation). Each of the charge D1 through D5 request that the Panel comment specifically on some aspect of these factors; D1 deals with incorporation of uncertainty, D2 with the most appropriate type of extrapolation to use, D3 with precision and accuracy of the NRC model, D4 with drinking water intake value, and D5 food intake value. The Panel responses to D1 and D2 are clearly responsive to the charge. For D3, D4, and D5 the responses, while framed in a very thorough manner, generally take the form of a commentary on what needs to be done before these questions can be answered (instead of answering the questions as asked).

For D3 the Panel found errors in the model, and made several good suggestions for improvement, but did not directly assess its accuracy and precision. It may be that such an assessment is not at present possible; if so then perhaps a statement to that effect could be made.

D4 asks the Panel to recommend a drinking water intake value based upon the Taiwanese data. Again the Panel pointed out additional needs in this area, including the incorporation of variability parameters, sensitivity analyses, distinguishing consumption by sex, and the need to include other As sources.

For D5 the Panel's again recommends more sensitivity analyses related to dietary intake.

All of these are good suggestions. When coupled with the responses to D1 and D2 (which also recommend sensitivity analyses and MCA), the overall impression is that the Panel is not prepared, at this time, to recommend specific values for intake of As. It further suggests that uncertainty and variability of exposure and sensitivity of exposed sub-populations will need to be factored into the ultimate recommendations. The Panel does not directly address the issue of variability in toxicological responses of an entire exposed population (preferring to focus on sensitive sub-populations as a way defining low-end exposure limits). In this context the Panel's approach does not challenge the Agency's preference against incorporating human toxicological uncertainty and variability into the analysis. One might argue that, by deriving standards based on variability in exposure parameters, and that are inclusive of the impacts on the most sensitive populations, the effect is similar. Perhaps so, but it would be a valuable exercise to compare standards derived in this way with those from a complete uncertainty analysis, inclusive of human toxicological responses.

(b) Clear and logical
Although I am not an expert in toxicology (and I defer to others on the Board with greater expertise on specific matters such as MOA and carcinogenesis) I found the report, in general, to be clear and readable. Knowing a bit about chemistry I found Figure 1 to be especially helpful.

(c) Supported conclusions
The Panel is to be commended for putting together a thoughtful, thorough, and scientifically defensible report. The conclusions appear sound, and the recommendations are supported by the accompanying material.

11. Dr. Valerie Thomas

The draft SAB arsenic review panel report addresses the original charge questions, and the conclusions and recommendations are supported by information in the body of the report.

In general the report is clear and logical. However, I find that the letter to the Administrator is not completely clear. Specifically, the paragraph on page 2, lines 4-19, could and should be rewritten so that it is easier to understand. The paragraph should make clear, perhaps by use of a heading, that it refers to the risk assessment of DMAv. In addition or alternatively, the paragraph would be more clear if the first sentence, lines 4-6, were simply cut. The detail is provided in the summary and the main text and does not need to be included in the

letter to the Administrator.

12. Dr. Robert Twiss

All charge questions OK pending results of teleconference discussion